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A New Synthetic Method of All Carboxylate-free DTPA Derivatives and its Application to the Synthesis of Gd-Carborane Complex

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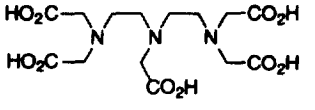
Abstract: All-carboxylate free DTPA derivatives, such as **10** and **15**, can be synthesized via the palladium catalyzed reaction of allylic carbonates (**9** and **13**) with **7**. This new methodology enables to synthesize a carborane containing Gd-DTPA complex **16** without losing one of all the five chelating carboxylates.

Diethylenetriaminepentaacetic acid (DTPA, **1**) is one of the most well-known chelating reagents for producing a stable complex with various heavy metal ions.[1] Bifunctional chelating agents based on DTPA are compounds that comprise both a powerful metal chelating group and a second functional group that can be a reactive moiety capable of forming covalent bonds with biological molecules or a hydrophobic aliphatic chain. A general method for coupling DTPA to the second functional group has included amide bond formation reaction between DTPA anhydride **2** and amines, which produces tetraacid derivatives **3** (Scheme1).[1] It has been pointed out that chemical modification of the carboxylate groups of DTPA causes to weaken metal-binding property and results in decreasing stability of the DTPA-chelating agent in vivo.[2] Accordingly, it is desirable to develop a method for preparing DTPA-bifunctional chelating agents in which a second functional group is attached to DTPA carbon framework through C–C bond (for example **4**). A number of bifunctional chelating reagents based on EDTA (ethylenediaminetetraacetic acid) have been prepared from p-aminobenzyl-EDTA **5** in which an amino functional group is bound to EDTA chelating group through C–C bond[2]. However, few DTPA derivatives having a second functional group at the carbon skeleton (such as **4**) have been synthesized.

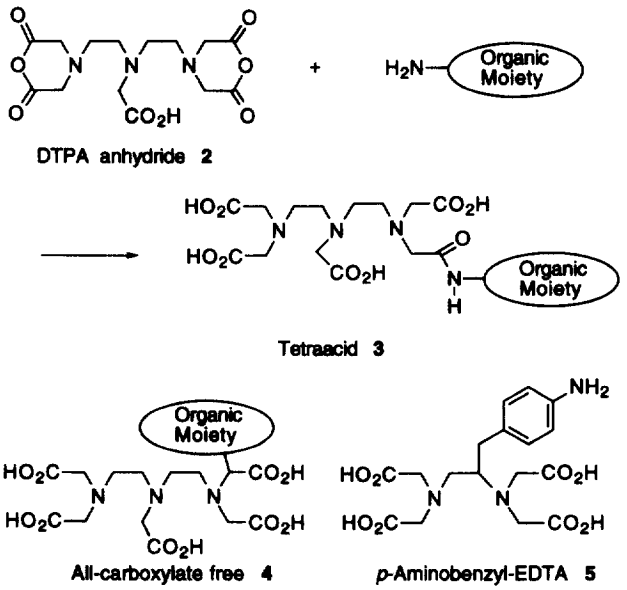


DTPA **1**

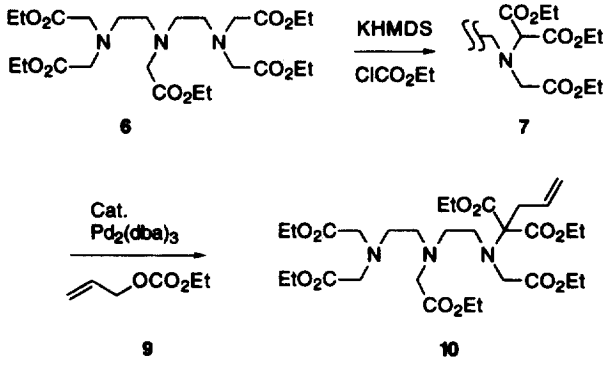
We wish to report a new synthetic method of all carboxylate free DTPA derivatives **4** via palladium catalyzed C–C bond formation reaction, and its application to the synthesis of a Gd–carborane complex. The pentaethyl ester **6** was prepared in 79% yield by refluxing **1** in ethanol in the presence of sulfonic acid. First we examined a carbanion formation at the α–position of the ester group of **6** followed by trapping with various electrophiles. After a number of trials[3], we found that the reaction of **6** with 2 equiv KHMDS in THF at -78C° followed by addition of 3 equiv ethyl chloroformate gave the mono–ethoxycarbonyl adduct **7** in 53%

yield without being accompanied with the di-carbonylated product **8**.[4] The use of 3 equiv. KHMDS and 3 equiv ethyl chloroformate produced a mixture of **7** and **8**, separation of which was difficult with column chromatography. With one equiv KHMDS and excess ethyl chloroformate, small amounts of **7** were obtained along with large amounts of **6** (>70%).[5]

Scheme 1. A General Method for Preparation of Bifunctional Chelating Agents Based on DTPA



Scheme 2. Synthesis of Pentacarboxylate-free DTPA Derivatives



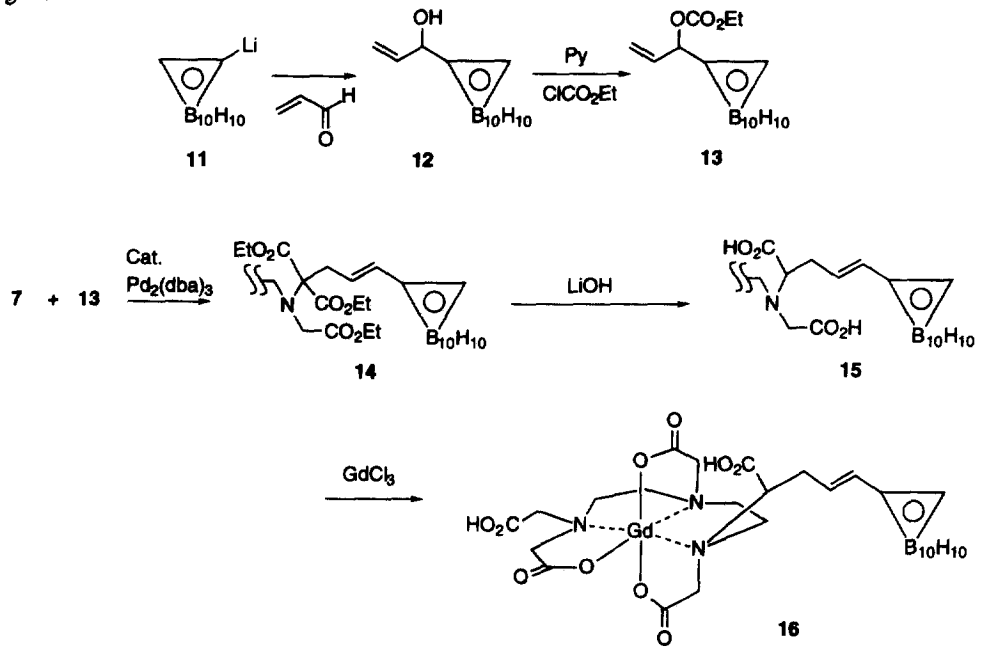
Since there is an acidic methyne proton in **7**, we attempted to extend carbon chain from the carbon via carbanionic route. The use of rather strong bases such as NaH caused complex ester condensations. With weak bases, such as K_2CO_3 (suspension) in acetone, no reaction occurred at room temperature. Finally we

found that the palladium catalyzed allylation [6] with allyl ethyl carbonate **9a**[7] gave the allylation product **10** in 80% yield. Among the catalysts examined, palladium bis(dibenzylideneacetone) / 1,2-bis(diphenylphosphino)ethane ($Pd_2(dba)_3$/dppe) system in THF gave the best result. [8]

The use of Ph_3P and trimethylolpropane phosphate (tmpp) as a ligand gave lower yield of **10**. THF was the best solvent; the reaction of **7** with **9** in the presence of $Pd_2(dba)_3$/ dppe in CH_3CN did not give **10** at all. Since an allylic moiety is attached as a second functional group via C-C bond, biological molecules can be bound to a metal chelating group without losing one of five carboxylate groups.

Much attention has been paid to ^{157}Gd-labelled DNA ligand as a Gd-carrier for neutron capture therapy.[9] On the other hand, it is well known that ortho-carborane is an important and useful structural unit for boron neutron capture therapy.[10] It occurred to us that a combination of ^{157}Gd and ^{10}B might enhance the efficiency of neutron capture therapy. We applied the synthetic method of all carboxylate free DTPA derivative to the synthesis of Gd-carborane complex.

Reaction of 1-lithio-orthocarborane **11** with acrolein in THF at -78°C gave **12** in 89% yield,[11] which was converted to **13** in quantitative yield upon treatment with ethyl chloroformate. The palladium catalyzed reaction of 1 equiv **7** with 3 equiv **13** gave **14** in 74% yield. Excess **13** was recovered, and can be used again as a starting material. Hydrolysis of all ethyl esters of **14** followed by decarboxylation was carried out with LiOH[12], giving the pentaacid **15** in 68% yield. Treatment of **15** with gadolinium(III) chloride afforded the desired Gd-carborane complex **16** in quantitative yield. Biological properties of **16** are now under investigation.



A key for the successful functionalization from **7** is the use of the palladium catalyzed allylation. Conventional carbanion based procedures led to self-condensation of the ester groups. Instead of simple allylcarbonate **9**, we can use allylcarbonates having biologically active moieties(for example **13**) or further manipulation from the allyl group of **10** may be possible. Consequently, we believe that all pentacarboxylate

free DTPA analogues **4** has the potential to become an attractive alternative for the previous amide-bonded tetraacid.

References

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3 Various electrophiles (benzyl bromide, methyl iodide, butyl iodide, acrolein, 4-cyanobenzyl bromide, and allyl bromide) in the presence of bases (LDA, NaHMDS, KHMDS) were examined, but complex mixture of products due to poly-alkylation and poly-ester-condensation were obtaind.

4 When NaHMDS was used instead of KHMDS, yield of **8** was increased. The structure of **8** was not clear because the position, at which the second ester group attached, could not be determined.

5 H_2N-CO_2Et, probably derived from $(Me_3Si)_2N$-CO_2Et, was obtained as a by-product.

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7 The palladium catalyzed reaction with allylic acetate did not give the desired product **10**.

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12 Sodium or potassium hydroxide did not work well.

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